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TITLE: Rescuing Our Warriors from Chronic Pain: A Battlefield-to-Nondeployment Means to Prevent Opioid-induced Amplification of Neuropathic Pain from Traumatic Injury

PRINCIPAL INVESTIGATOR: Linda R. Watkins, Ph.D.

CONTRACTING ORGANIZATION: Regents of the University of Colorado
Boulder, CO 80303

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Linda R Watkins, Ph.D.
Peter M Grace, Ph.D.
Suzanne M Fulgham, M.S.

E-Mail: linda.watkins@colorado.edu

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14. ABSTRACT

Based on our preliminary data and a thorough review of the available scientific/clinical literature to date, *we hypothesize that:* (**a**) Trauma and opioids combine to amplify the intensity and duration of trauma-induced chronic pain. (**b**) This combined exposure to trauma plus opioids amplifies the creation and release of endogenous danger signals in spinal cord that create enduring release of TLR4 stimulatory substances as a consequence of cell stress/damage/death, leading to amplified trauma induced chronic pain.

Objective 1. Define the response to opioids commonly used for acute pain management, when these are administered early after trauma, prior to development of neuropathic pain

Objective 2. Define the response to opioids & non-opioids commonly used for neuropathic pain management, when these treatments are administered later after trauma, after development of neuropathic pain

Objective 3. Define whether the deleterious effects on neuropathic pain observed in Aims 1 & 2 can be prevented by targeting TLR4 and P2X7

Objective 4. Define whether the deleterious effects of analgesics, and positive effects of co-administered TLR4/P2X7 antagonists, extend beyond neuropathic pain to other indices of disability

15. SUBJECT TERMS chronic pain, opioid analgesics, non-opioid analgesics, toll-like receptor 4, return to duty					
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1. Introduction

In the year two of the project we have extended our investigation of the impact of a short course of morphine on the amplification of neuropathic pain to investigate two additional opioids, Fentanyl and Oxycodone and to the non-opioid (tricyclic) amitriptyline. We have investigated the effects of opioid administration at various time points after injury, the acute period (one hour) after trauma, at the development of chronic pain (day 10 post-trauma), or late in the time course when chronic pain is well established (one month post-trauma). We have demonstrated that Fentanyl and Oxycodone also amplify the intensity and duration of chronic pain when administered after the development of chronic pain, at day 10 or one month after injury. The amplification of neuropathic pain following the administration of other opioids beyond morphine suggests a similar mechanism, involving opioid induced activation of TLR4 receptors prolonging inflammatory signaling, and delaying recovery (Watkins, Hutchinson, Rice, Maier, Trends Pharmacol Sci., 2009). In year three of this project we will explore whether amitriptyline has a pain amplifying effect and if co-administration of the TLR4 antagonist (+)-Naloxone, and the P2X7 antagonist A438079 can improve the neuroinflammatory consequences of these opioids, leading to an expedited resolution of neuropathic pain.

2. Keywords

Neuropathic pain, opioid analgesics, non-opioid analgesics, return to duty, morphine, oxycodone, fentanyl, toll-like receptor 4, P2X7

3. Accomplishments:

What were the major goals of the project?

1. Test if antagonists administered with morphine prevent opioid induced suppression of voluntary wheel running. Rats were habituated to running wheels with free access for 7 days, and baseline running data were collected. Rats then received 4 suture CCI surgeries or sham surgeries of the sciatic nerve. At day 10 post CCI rats received a 5-day course of morphine (5 mg/kg b.i.d.) or saline, along with the TLR4 antagonist (+)-Naloxone (20-mg/kg s.c.), the P2X7 antagonist A438079 (1-mg/kg s.c.), or equivolume s.c. saline vehicle. Running

data were collected by computer 24 hours per day, 7 days a week. Task 10, Aim 3B

2. Test if the opioids Fentanyl and Oxycodone given at day 10 post trauma induce potentiation of neuropathic pain. All rats received CCI surgeries of the sciatic nerve with one 6-0 suture. At day 10 post CCI rats began a 5-day course of Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg), or saline control. Assessment of mechanical allodynia by Von Frey testing occurred at day one post opioid completion and weekly thereafter. Task 5, Aim 2A

3. Test if the opioids Fentanyl and Oxycodone given at week four post trauma induce potentiation of neuropathic pain. All rats received CCI surgeries of the sciatic nerve with one 6-0 suture. At week four post CCI rats began a 5-day course of Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg), or saline control. Assessment of mechanical allodynia by Von Frey testing occurred at day one post opioid completion and weekly thereafter. Task 7, Aim 2C

4. Test if the opioids Fentanyl and Oxycodone given at one hour post trauma induce potentiation of neuropathic pain. All rats received CCI surgeries of the sciatic nerve with one 6-0 suture. At one hour post CCI rats began a 5-day course of Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg), or saline control. Assessment of mechanical allodynia by Von Frey testing occurred at day one post opioid completion and weekly thereafter. Task 3, Aim 1B; Task 4, Aim 1C

5. What was accomplished under these goals?

1. Test if antagonists administered with morphine prevent opioid induced suppression of voluntary wheel running. Task 10, Aim 3B

This experiment tested whether administration of the TLR4 antagonist (+)-Naloxone and the P2X7 antagonist A438079 improve voluntary running behavior when administered along with morphine or saline at day 10 post trauma. Rats were habituated to running wheels with free access for 7 days, and baseline running data were collected. Rats then received 4 suture CCI surgeries or sham surgeries of the sciatic nerve. At day 10 post CCI rats received a 5-day course of morphine (5 mg/kg b.i.d.) or saline, along with the TLR4 antagonist (+)-Naloxone (20-mg/kg s.c.), the P2X7 antagonist A438079 (1-mg/kg s.c.), or equivolume s.c. saline vehicle. Running data were collected by computer 24 hours per day, 7 days a week. These experiments revealed a significant, lasting decrease of voluntary wheel running due to chronic pain in rats that received CCI

surgery compared to rats that received sham surgeries. (Figure 1 and 2). In these experiments we did not replicate the effect of morphine suppression of voluntary wheel running observed in our preliminary experiments on parameters of distance traveled or maximum running speed (Figure 3 and 4). This suggests that in this outcome measure of voluntary running behavior as measure of return to duty behavior, there may be no consistent, significant long term effects of morphine. Both antagonists, (+)-Naloxone and A438079, were found to increase voluntary wheel running distance and speed following injury in rats that received morphine after injury (Figure 6 and 8), but not in rats that received saline after injury (Figure 5 and 9). Area Under Curve analysis for running distance is presented in Figure 7, speed in Figure 10. The improvement in voluntary wheel running in morphine treated rats that also received antagonists may be due to synergistic effects of decreased inflammatory signaling post injury combined with opioid analgesia.

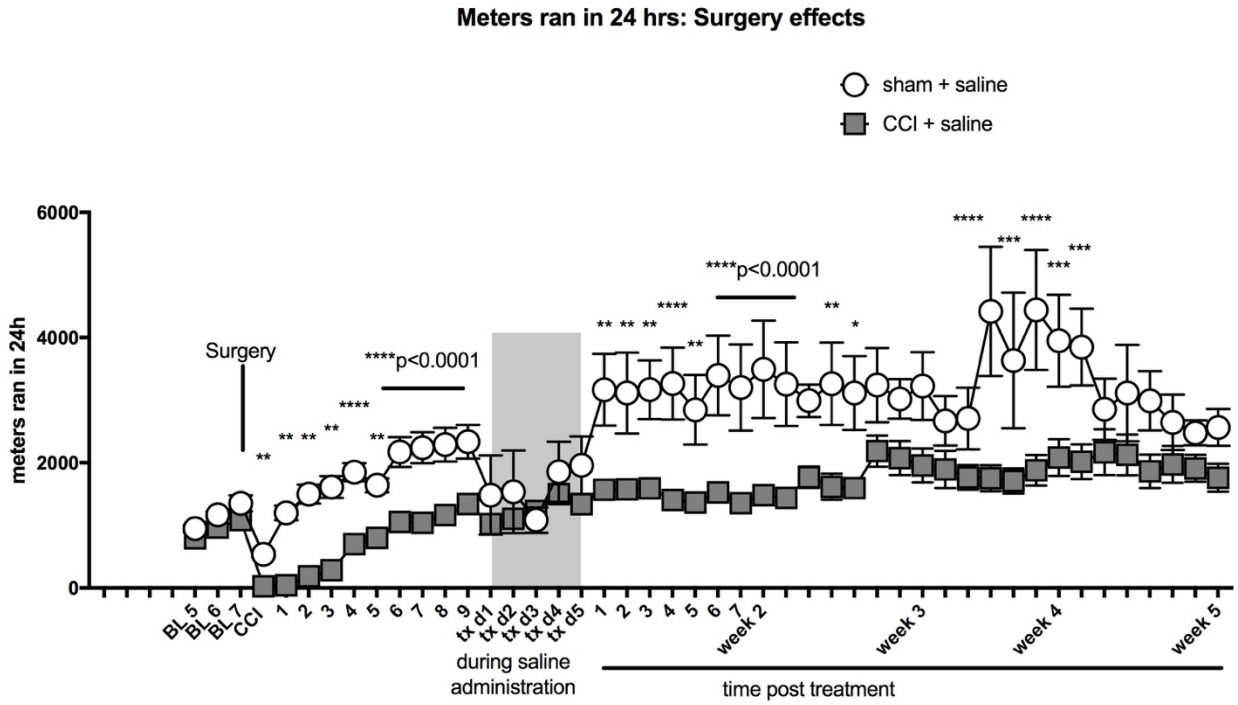


Figure 1. Chronic Constriction Injury (CCI) or sham surgeries were performed. Running data of meters ran were collected by computer 24 hours per day. Significant decreases in voluntary running behavior were observed in rats that received CCI surgeries for up to week 4 post injury. (Main effect surgery $p<0.0001$, main effect time $p<0.0001$, interaction $p<0.0001$, Two Way ANOVA, n=12-14/group CCI).

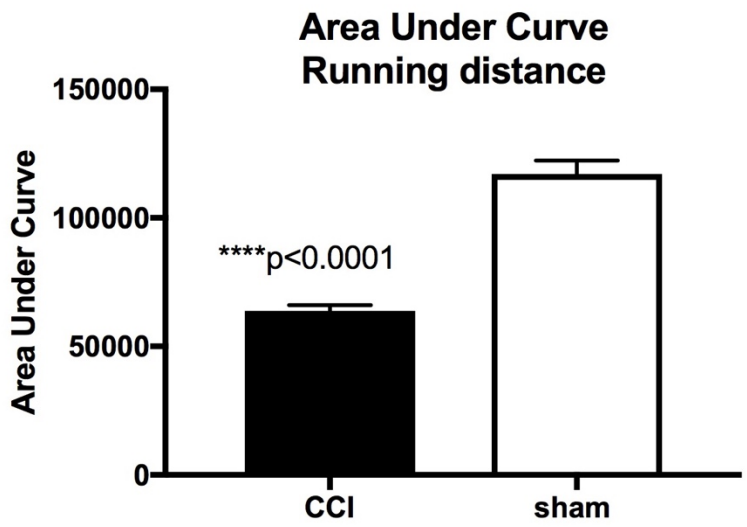


Figure 2. Area Under Curve of Meters ran in 24 hrs post surgery. p<0.0001 unpaired t test of Area Under Curve, n=12-14/group CCI,

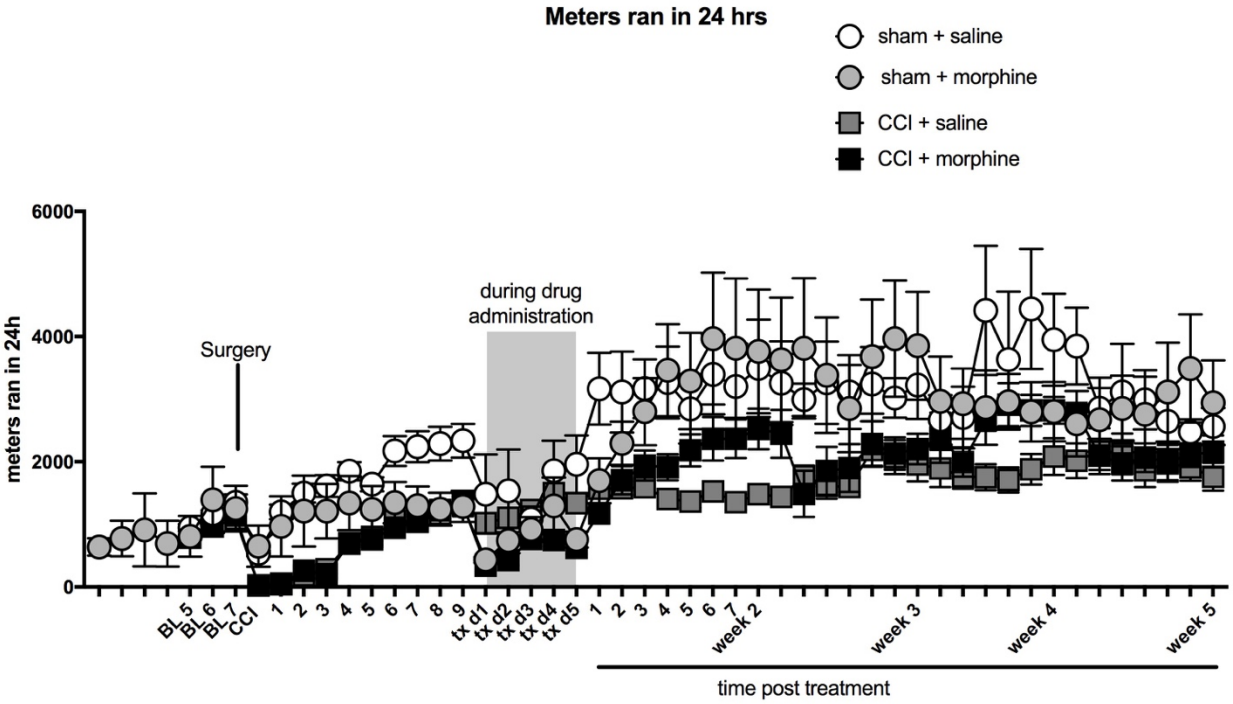


Figure 3. At day 10 post-surgery a 5 day course of morphine (5-mg/kg b.i.d.) or saline was given. Running data of meters ran were collected by computer 24 hours per day.. Main effect treatment p<0.0001, main effect time p=.12, interaction p=.77 Two Way ANOVA, n=14 CCI groups, n=6 sham groups. No significant decrease in running distance was observed in rats that received morphine vs saline following CCI surgery.

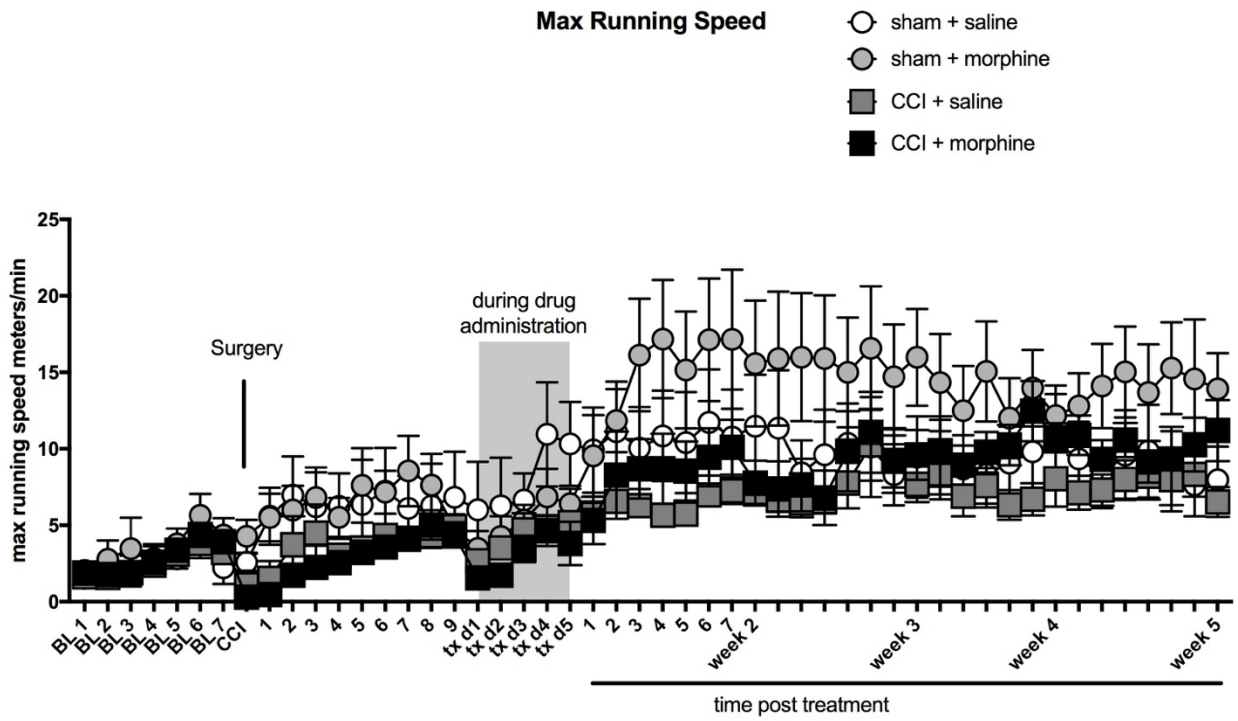


Figure 4. At day 10 post-surgery a 5 day course of morphine (5-mg/kg b.i.d.) or saline was given. Running data of maximum running speed were collected by computer 24 hours per day. No significant changes in maximum running speed were found following treatment with morphine compared to saline in CCI groups. Rats that received sham surgery + morphine showed increased running speed compared to CCI groups. Main effect drug $p<0.0001$, main effect time $p<0.0001$, interaction $p=.75$ Two Way ANOVA, n=14 CCI groups, n=6 sham groups

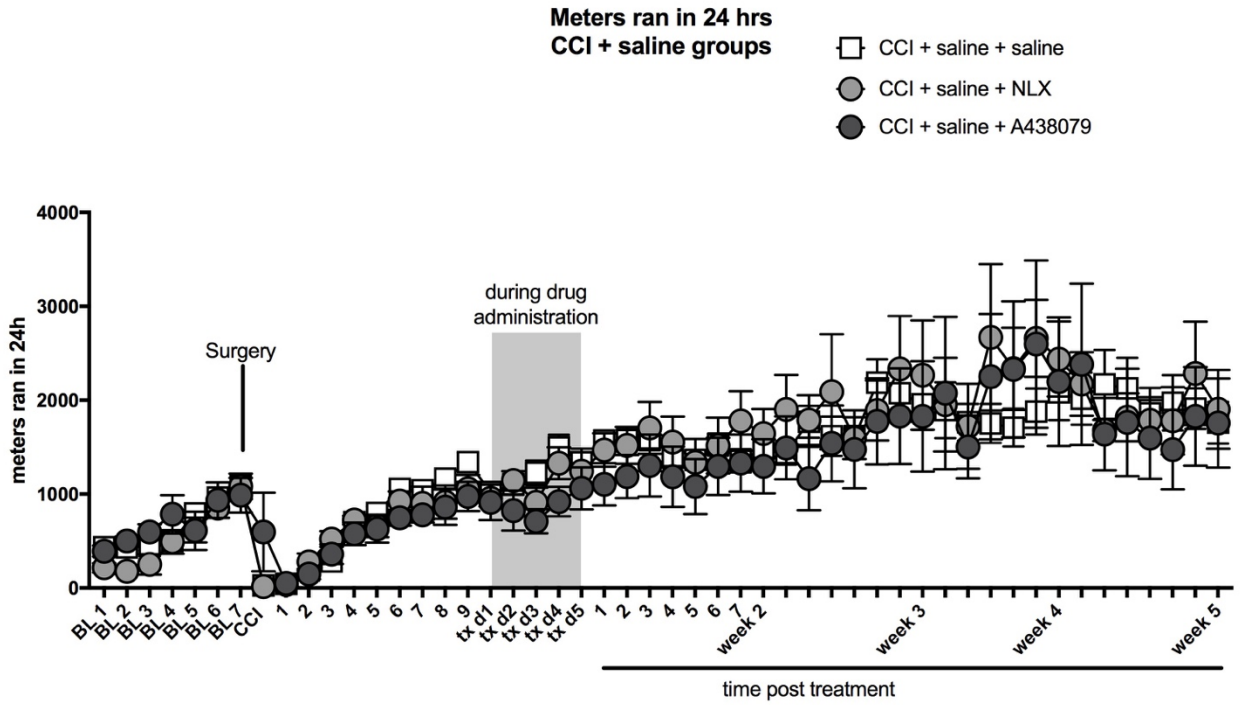


Figure 5. At day 10 post-surgery a 5 day course of saline was given, along with the TLR4 antagonist (+)-Naloxone (20-mg/kg), the P2X7 antagonist A438079 (1-mg/kg), or saline vehicle. Running data of meters ran were collected by computer 24 hours per day. Treatment with the TLR4 antagonist (+)-Naloxone, and the P2X7 antagonist A438079 did not alter running distance in rats that received saline following surgery. n=5-6/group.

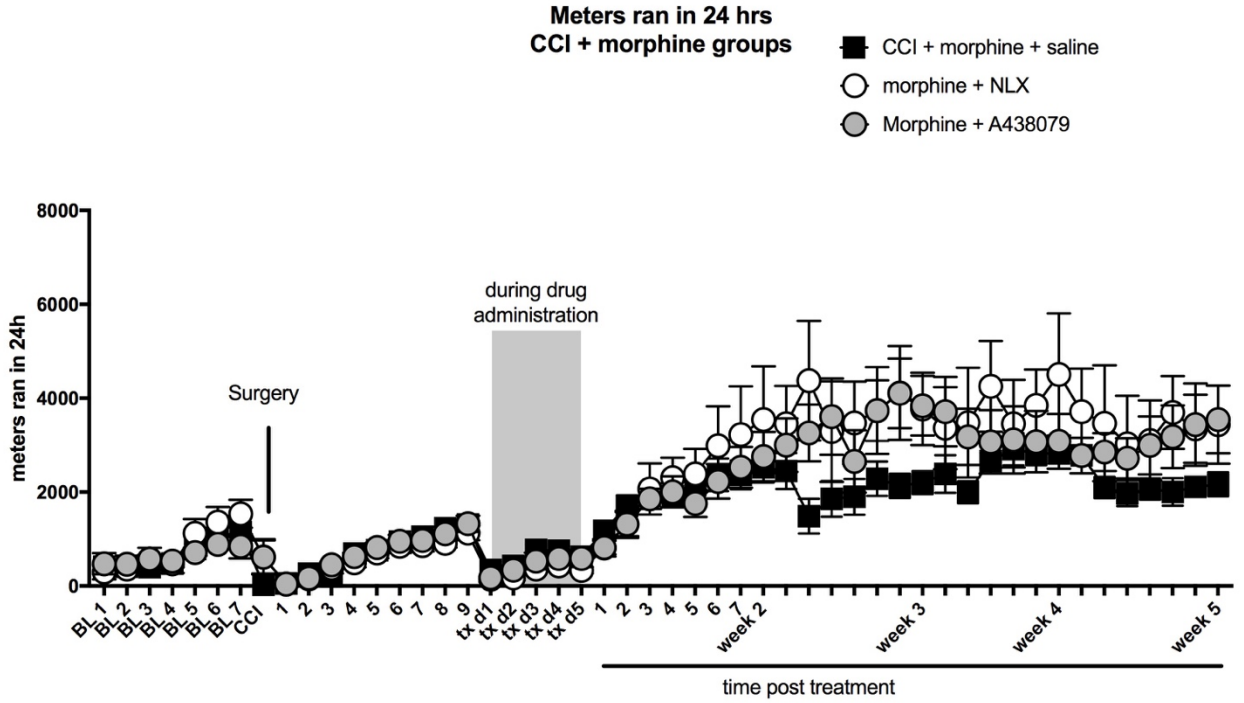


Figure 6. At day 10 post-surgery a 5 day course of morphine (5-mg/kg b.i.d.) was given, along with the TLR4 antagonist (+)-Naloxone (20-mg/kg), the P2X7 antagonist A438079 (1-mg/kg), or saline vehicle. Running data of meters ran were collected by computer 24 hours per day. Treatment with the TLR4 antagonist (+)-Naloxone, and the P2X7 antagonist A438079 increased running distance in rats that received morphine following surgery. ((Main effect of treatment $p<0.0001$, main effect time $p<0.0001$, interaction $p=.10$, Two Way ANOVA, n=5-6/group).

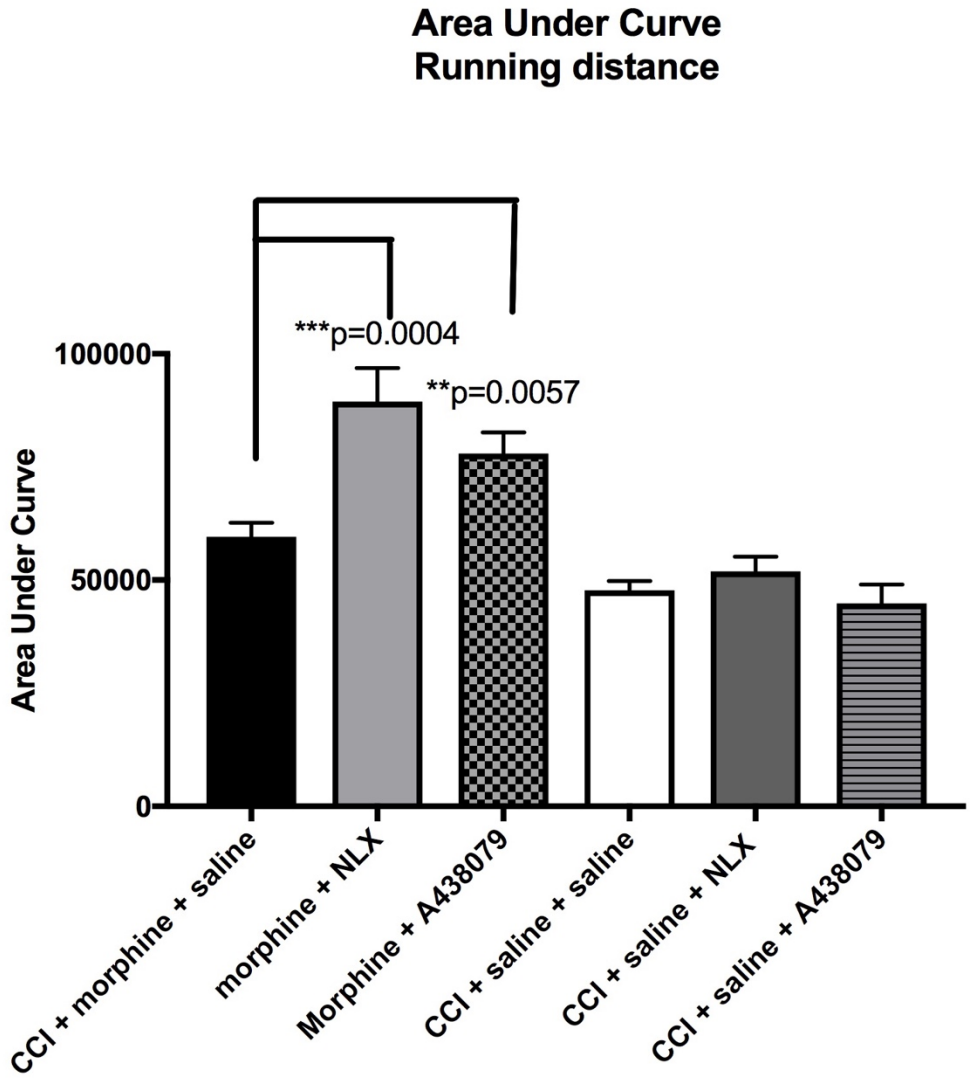


Figure 7. Area Under the Curve analysis of running distance post treatment. CCI+Morphine+ Saline vs CCI+Morphine+NLX $p=0.0004$ unpaired t test of Area Under Curve, n=5-6/group, CCI+Morphine+Saline vs CCI+Morphine+A438079 $p=0.0057$ unpaired t test of Area Under Curve, n=5-6/group

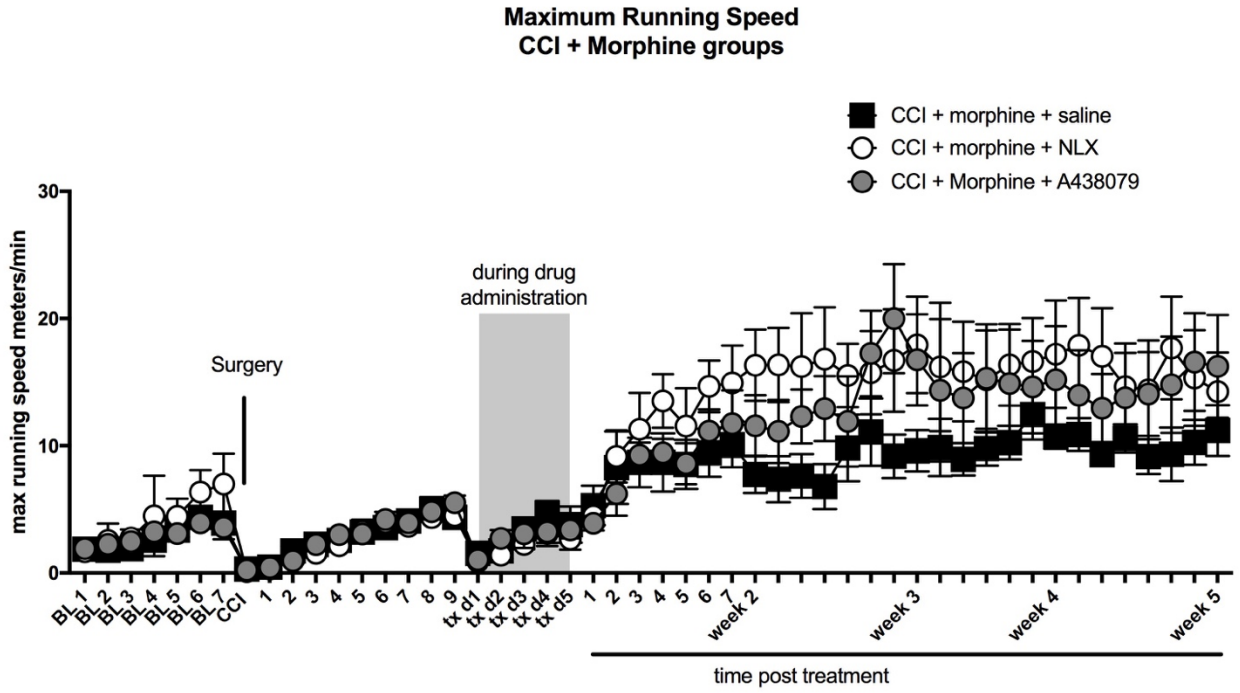


Figure 8. At day 10 post-surgery a 5 day course of morphine (5-mg/kg b.i.d.) was given, along with the TLR4 antagonist (+)-Naloxone (20-mg/kg), the P2X7 antagonist A438079 (1-mg/kg), or saline vehicle. Maximum running speed data was collected by computer 24 hours per day. Treatment with the TLR4 antagonist (+)-Naloxone, and the P2X7 antagonist A438079 increased running speed in rats that received morphine following surgery. (Main effect of treatment $p<0.0001$, main effect time $p<0.0001$, interaction $p=.49$, Two Way ANOVA, n=5-6/group).

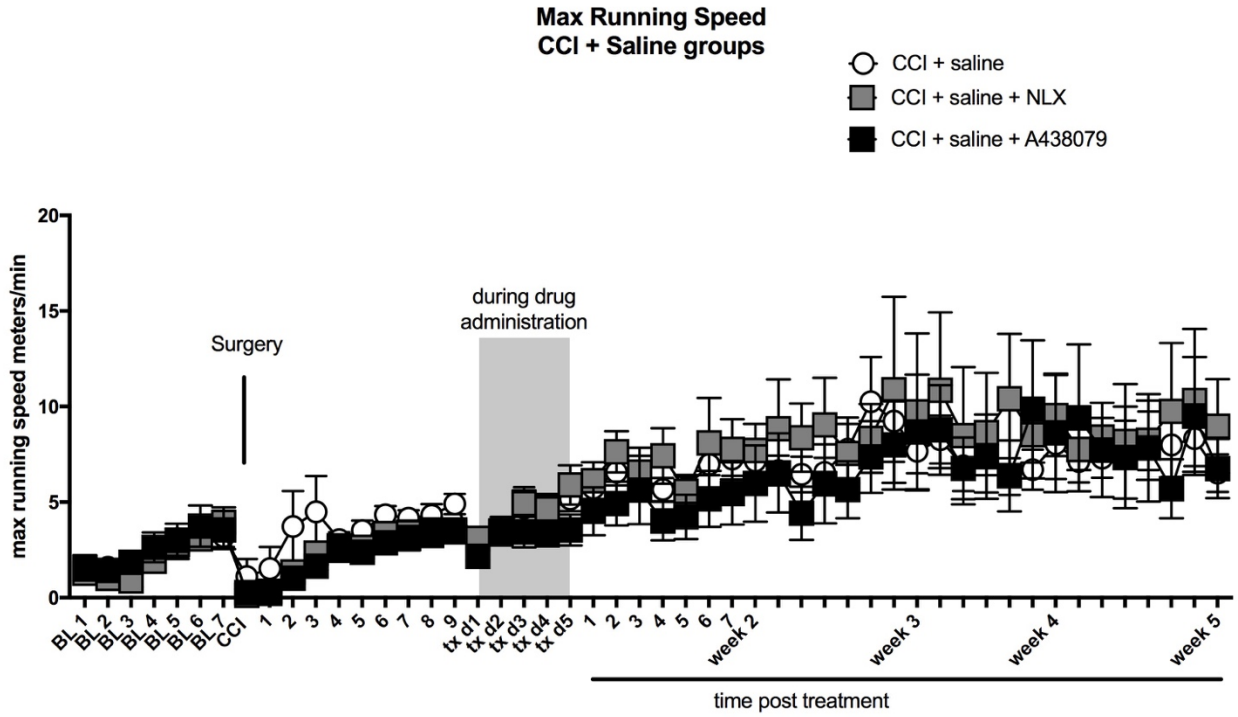


Figure 9. At day 10 post-surgery a 5 day course of saline (5-mg/kg b.i.d.) was given, along with the TLR4 antagonist (+)-Naloxone (20-mg/kg), the P2X7 antagonist A438079 (1-mg/kg), or saline vehicle. Maximum running speed data was collected by computer 24 hours per day. No significant effects on running speed were observed in rats that received saline along with either antagonist following CCI surgery, n=5-6/group).

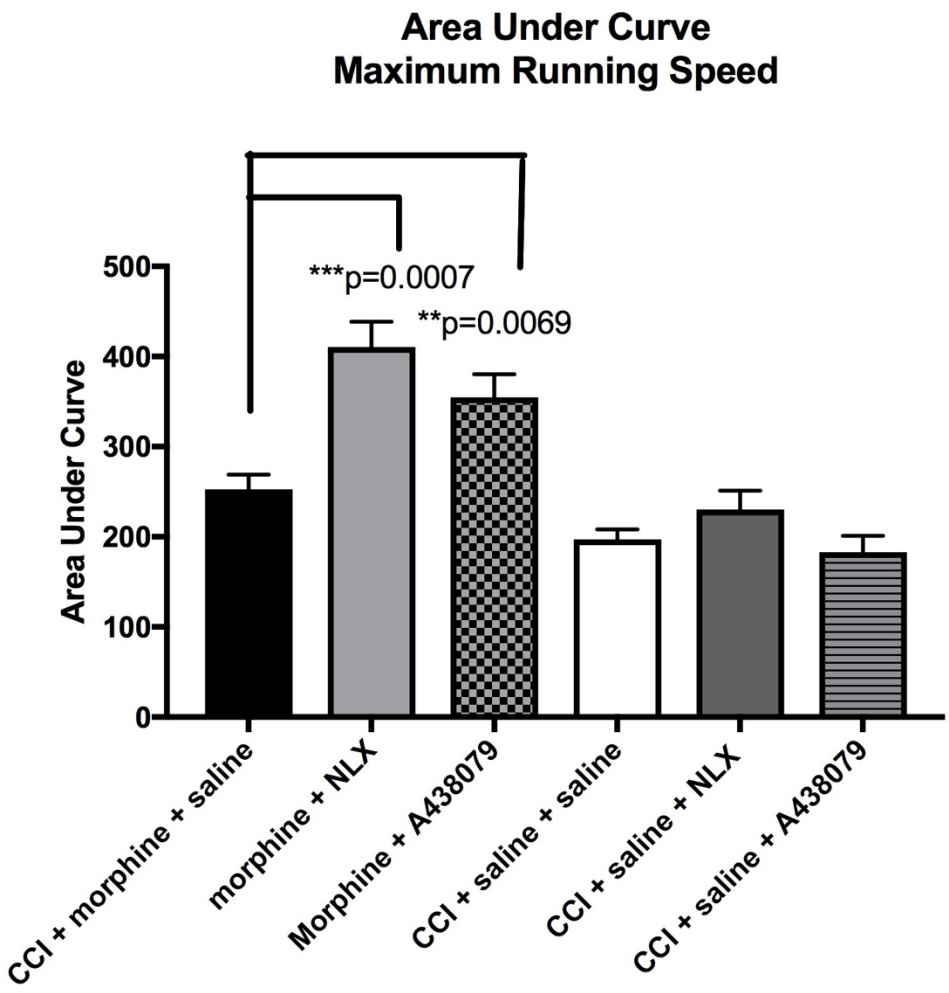


Figure 10. Area Under Curve of maximum running speed post treatment. CCI+Morphine+Saline vs CCI+Morphine+NLX p=0.0007 unpaired t test of Area Under Curve, n=5-6/group, CCI+Morphine+Saline vs CCI+Morphine+A438079 p=0.0069 unpaired t test of Area Under Curve, n=5-6/group

2. **Test if the opioids Fentanyl and Oxycodone given at day 10 post trauma induce potentiation of neuropathic pain. Task 5, Aim 2A**

The opioids Fentanyl and Oxycodone were tested to determine whether the potentiation of pain seen after a short course of morphine at this time point also extends to other commonly used opioids. All rats received CCI surgeries of the sciatic nerve with one 6-0 suture. At day 10 post CCI, rats began a 5-day course of Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg), or saline control. Assessment of mechanical allodynia by Von Frey testing occurred at day one post opioid completion and weekly thereafter. Rats

given both opioids, Fentanyl and Oxycodone responded with lower pain thresholds (i.e. higher pain responsivity) than rats given saline. Results of this experiment are presented in Figure 11. Area Under Curve analysis is presented in Figure 12. These data suggest that in addition to morphine, other opioids administered at the time of chronic pain development can worsen pain outcome, suggesting a similar underlying mechanism.

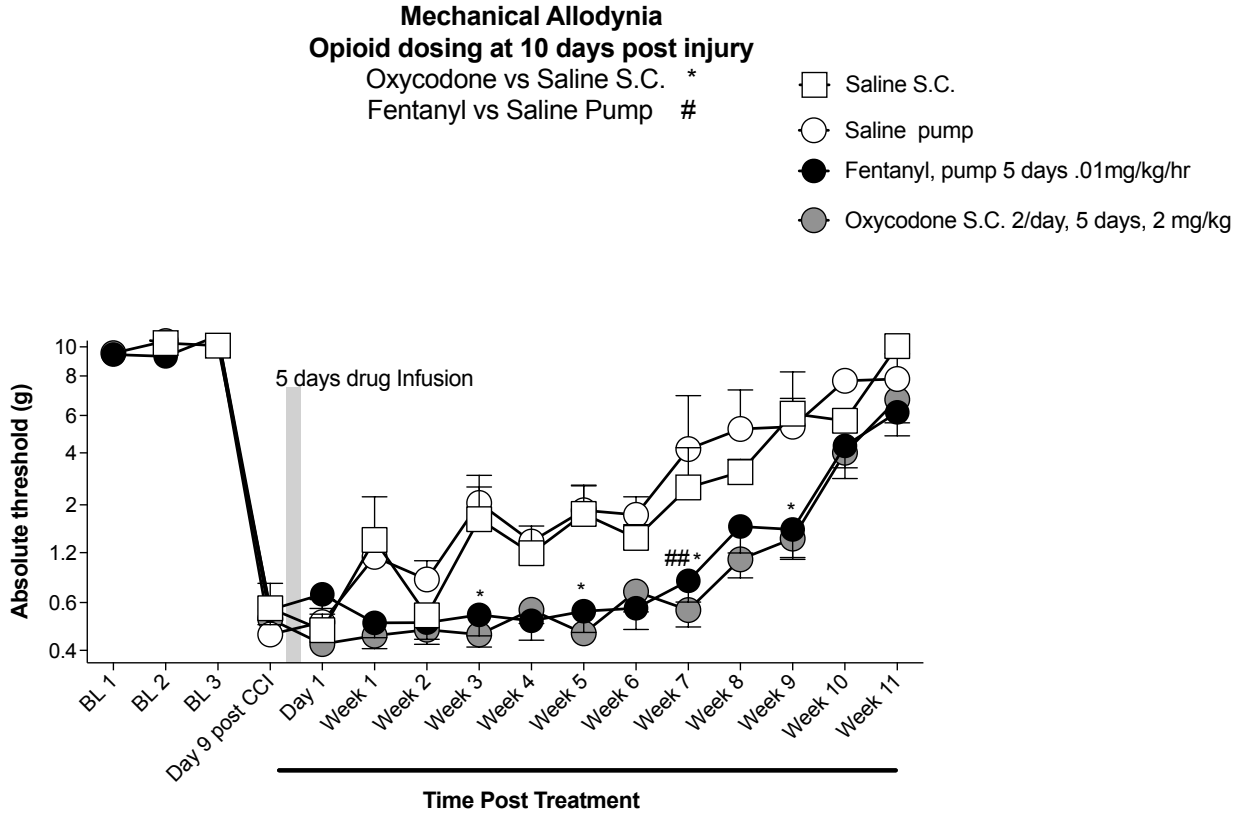


Figure 11. Chronic Constriction Injury (CCI) or sham surgeries were performed with one 6-0 suture. Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg) or saline were administered 10 days post-surgery for 5 days. Behavior testing was conducted at day 1 post opioid completion, and weekly thereafter. (Main effect drug $p<0.0001$, Main effect time $p<0.0001$, interaction $p<0.0003$, Two Way ANOVA, Tukey Post hoc analysis saline vs Oxycodone $p<0.05$ week 4,6; $p<0.005$ week 1; $p<0.0001$ week 3,5,7,8,9 post treatment. Tukey Post hoc analysis saline vs Fentanyl , $p<0.05$ week 1, 4; $p<.005$ week 6, 8; $p<0.0005$ week 3,5; $p<0.0001$ week 7, 9, post treatment n=6/group opioids, n=4/group saline)

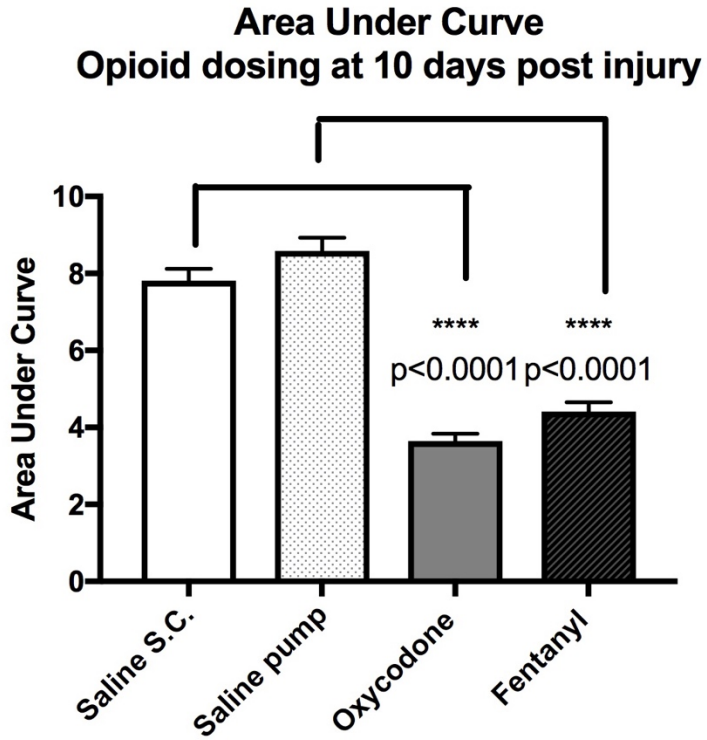


Figure 12. Area Under Curve of mechanical allodynia post treatment. Chronic Constriction Injury (CCI) or sham surgeries were performed with one 6-0 suture. Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg) or saline were administered at 10 days post-surgery for 5 days. Behavior testing was conducted at day 1 post opioid completion, and weekly thereafter. (Oxycodone and Fentanyl vs saline $p<0.0001$, unpaired t test of Area Under Curve, n=6/group opioids, n=4/group saline)

3. **Test if the opioids Fentanyl and Oxycodone given at week four post trauma induce potentiation of neuropathic pain. Task 7, Aim 2C**

In previous experiments we found that morphine given at a late time point (four weeks) after trauma also increased the magnitude of neuropathic pain. In this experiment we tested whether the opioids Fentanyl and Oxycodone produced this same effect when dosing begins at this late time point. All rats received CCI surgeries of the sciatic nerve with one 6-0 suture. At week four post CCI rats began a 5-day course of Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg), or saline control. As no difference was found between

subcutaneous administration of saline by injection compared to osmotic pump in the previous experiment, all saline was administered by osmotic pump in this experiment. This controls for the most invasive administration of drug, surgical implant. Assessment of mechanical allodynia by Von Frey testing occurred at day one post opioid completion and weekly thereafter. Rats given either opioid (Fentanyl or Oxycodone) responded with lower pain thresholds (i.e. higher pain responsivity) than rats given saline at this late time point (Main effect drug $p<0.0001$, Main effect time $p<.0001$, interaction $p<0.0001$, Two Way ANOVA, Tukey Post hoc analysis saline vs Oxycodone $p<0.0001$ week 6,7,8,9,11 post treatment, $p<0.0005$ week 10 post treatment, n=8/group opioids, n=4/group saline). Results of this experiment are presented in Figure 13. Area Under Curve analysis is presented in Figure 14. These data suggest that in addition to morphine, other opioids administered even late after the onset of chronic pain development can worsen pain outcome, prolonging recovery.

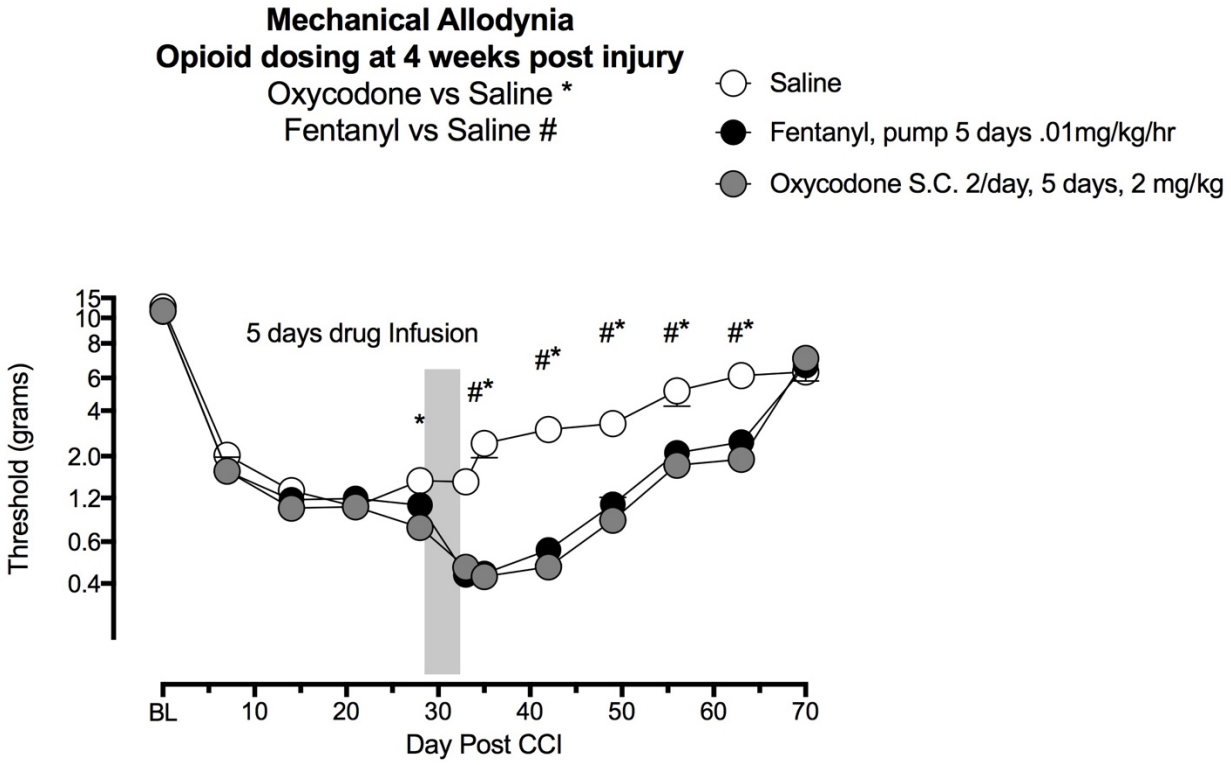


Figure 13. Chronic Constriction Injury (CCI) or sham surgeries were performed with one 6-0 suture. Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg) or saline were administered at four weeks post-surgery for 5 days. Behavior testing was conducted at day 1 post opioid completion, and weekly thereafter. (Main effect drug $p<0.0001$, Main effect time $p<0.0001$, interaction $p<0.0001$, Two Way ANOVA, Tukey Post hoc analysis saline vs

Oxycodone p<0.0001 week 6,7,8,9,11 post treatment, p<0.0005 week 10 post treatment, n=8/group opioids, n=4/group saline).

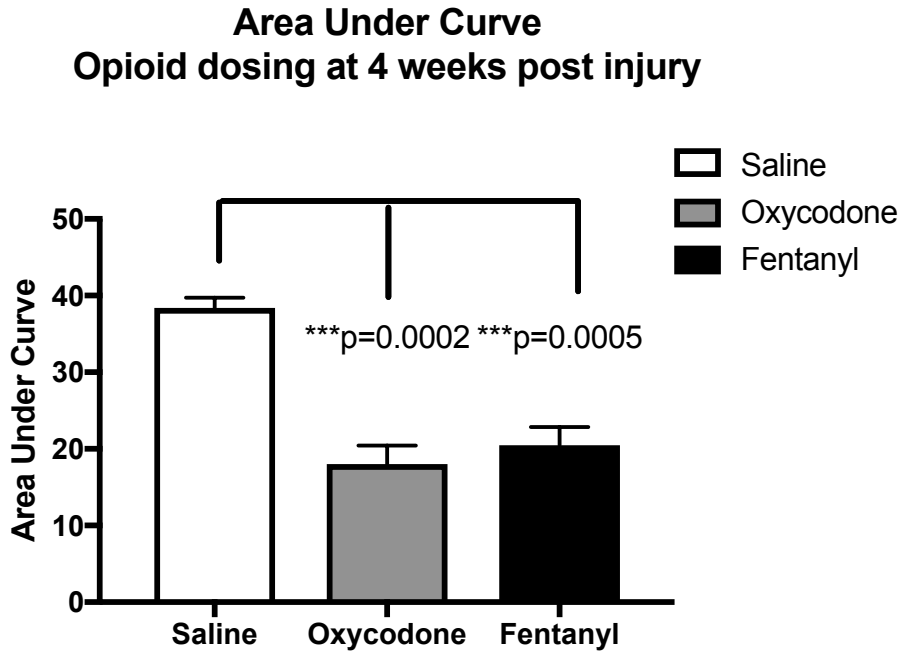


Figure 14. Chronic Constriction Injury (CCI) were performed with one 6-0 suture. Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg) or saline were administered at four weeks post-surgery for 5 days. Behavior testing was conducted at day 1 post opioid completion, and weekly thereafter. (Oxycodone vs saline p=0.0002, Fentanyl vs saline p=0.0005, unpaired t test of Area Under Curve, n=8/group opioids, n=4/group saline.)

4. **Test if the opioids Fentanyl and Oxycodone given at one-hour post trauma induce potentiation of neuropathic pain. Task 3, Aim 1B; Task 4, Aim 1C**

In previous experiments we found that morphine given at an early time point (one-hour) after trauma also increased the magnitude of neuropathic pain, to a lesser extent than when administered after the development of chronic pain. In this experiment we tested whether the opioids Fentanyl and Oxycodone produced this same effect when dosing begins at this early time point. All rats received CCI surgeries of the sciatic nerve with one 6-0 suture. At one-hour post CCI rats began a 5-day course of Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg), or saline control. Assessment of mechanical allodynia by Von Frey testing occurred at day one post opioid completion and weekly thereafter. We did not find a significant effect of opioids on mechanical allodynia at this time point. Results of this experiment are presented in Figure 15. Area Under Curve analysis is presented in Figure 16.

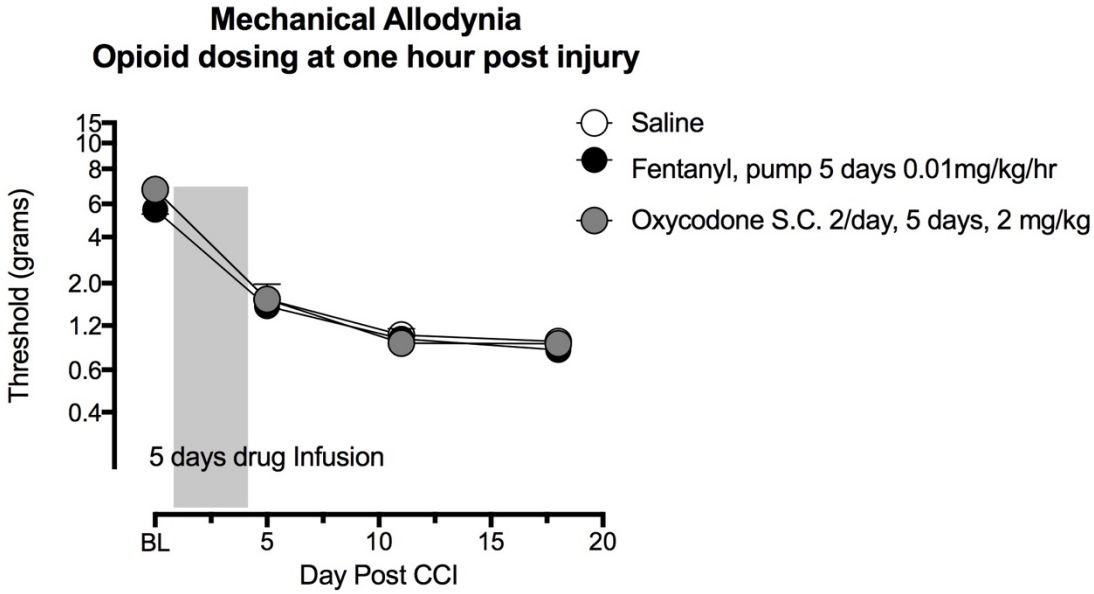


Figure 15. Chronic Constriction Injury (CCI) were performed with one 6-0 suture. Fentanyl (0.01 mg/kg/hr), Oxycodone (2 mg/kg) or saline were administered at one hour post-surgery for 5 days. No significant differences were found between groups. n=8/group

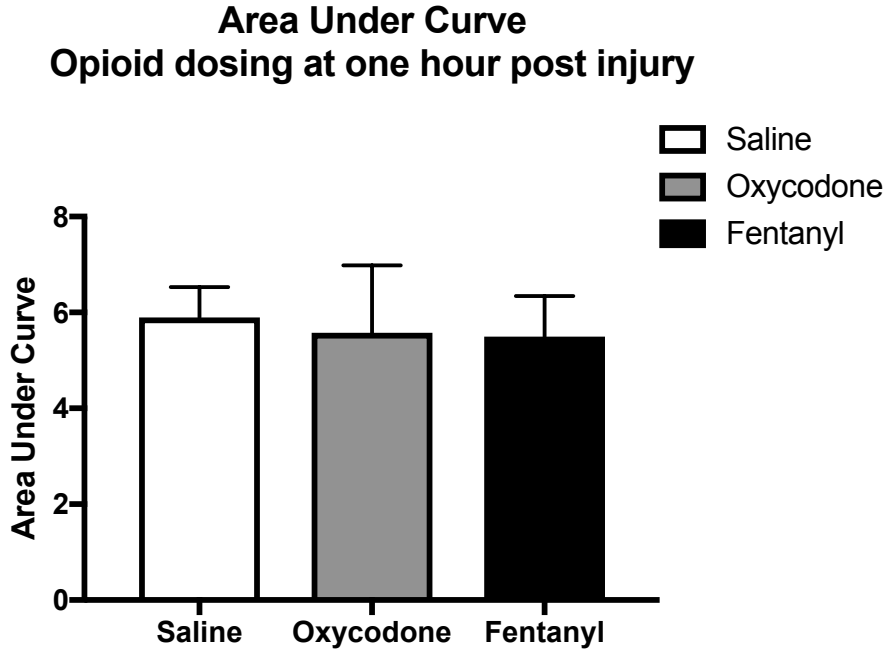


Figure 16. Area Under Curve of mechanical allodynia post treatment. Chronic Constriction Injury (CCI) were performed with one 6-0 suture. Fentanyl (0.01 mg/kg/hr),

Oxycodone (2 mg/kg) or saline were administered at one hour post-surgery for 5 days. No significant differences were found between groups. n=8/group

What opportunities for training and professional development has the project provided?

This project provided opportunities for the professional research associates to advance professional skills such as Von Frey testing for mechanical allodynia, a skill that takes time and repetition to master. Research associates also advanced skills in data collection and analysis for the new Lafayette Instruments system of running wheels used to analyze morphine and antagonist effects on voluntary running behavior.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

Task 8 (Aim 2D) will be completed. Amitriptyline will be dosed 1 month after trauma. Behavioral testing (VF) every 3-7 days until all rats return to baseline thresholds.

Task 10 (Aim 3B) will be started. Opioids/non-opioids plus antagonists: dosing starts 10 days after trauma. Behavioral testing (VF) every 3-7 days until all rats return to baseline thresholds

Task 13 (Aim 4B) will be completed. Opioids on “return to duty”: dosing starts 10 days after trauma. CCI vs. sham surgery preceded by baseline voluntary wheel running the week prior to surgery; begin co-administered opioids and antagonists 10 days after surgery, continuing for 5 days. Behavioral testing (wheel running) daily starting upon completion of drug doses until all rats return to baseline thresholds.

IMPACT:

What was the impact on other disciplines?

Nothing to report.

- **What was the impact on technology transfer?**

  Nothing to report.

- **What was the impact on society beyond science and technology?**

The results of this project could have implications for the treatment of chronic pain in veterans, military service members, and non-military general population. Peripheral nerve trauma can result in neuropathic pain that is debilitating and difficult to treat. Virtually all trauma patients receive opioids as the first therapeutic action after injury. Our data suggest that treatment with the opioids morphine, oxycodone, and fentanyl prolongs the duration and intensity of neuropathic pain whether opioid administration is at the time of chronic pain development, or up to one month after injury. Our early results with amitriptyline predict that the problem with opioids in enhancing chronic pain long term may be able to be circumvented by using amitriptyline instead of opioids for neuropathic pain treatment.

CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

The CU Boulder Department of Psychology moved to a new facility in early 2018. Some down time in experiments occurred during this move as the new lab, colony rooms, surgery space, and behavioral space was setup. Experiments were underway as soon as new space was decontaminated, inspected by IACUC and approved. Pilot studies were conducted to assure replication of previous paradigms since results in animal behavior can sometimes vary under different colony and behavioral conditions. All pain model and opioid paradigms replicated with success, and experiments were back underway with very little delay.

Dr Peter Grace has had significant delays in instituting his behavioral research program at MD Anderson Cancer Center. These include the absence of space required to reliably conduct behavioral experiments. Despite multiple attempts to have space allocated for his research, this was still not achieved after 18 months. Dr. Grace then requested an administrative transfer to another, more supportive department. This was granted in July 2018. Since then, Dr. Grace has been assigned 2 rooms with sufficient space to perform behavioral experiments. He has now finished outfitting them with his custom equipment. These substantial delays prevented him from materially contributing to this project.

In addition, Dr. Grace learned that the Office of Research Administration (ORA) did not submit the ACURO application in January 2017 when he sent it to them. They did not communicate this. Upon discovering this, Dr. Grace immediately requested that the application be submitted and working with ORA to resolve this issue.

Once the ACURO submission is approved, he will be positioned to complete the majority of studies proposed for Year 3.

Changes that had a significant impact on expenditures

Nothing to report.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  Nothing to report.
- **Significant changes in use or care of human subjects**

  Nothing to report.
- **Significant changes in use or care of vertebrate animals.**

  Nothing to report.
- **Significant changes in use of biohazards and/or select agents**

  Nothing to report.

PRODUCTS:

Nothing to Report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name: Linda R. Watkins, Ph.D.
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): none
Nearest person month worked: 10% effort for this quarter (no funds utilized)
Contribution to Project: Principal Investigator

Name: Peter M. Grace, Ph.D.
Project Role: Co- Principal Investigator
Researcher Identifier (e.g. ORCID ID): orcid.org/0000-0002-8999-1220
Nearest person month worked: 1% effort for this quarter (no funds utilized)
Contribution to Project: Co-Principal Investigator

Name: Suzanne M. Fulgham, M.S.
Project Role: Professional Research Assistant
Researcher Identifier (e.g. ORCID ID): none
Nearest person month worked: 3
Contribution to Project: Suzanne conducted experiments and analyzed data

Name: Jayson B. Ball, B.A.
Project Role: Professional Research Assistant
Researcher Identifier (e.g. ORCID ID): none
Nearest person month worked: 3
Contribution to Project: Jayson conducted experiments

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

1. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:** *For collaborative awards, independent reports are required from **BOTH** the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A*

report shall be submitted to https://ers.amedd.army.mil for each unique award.

- **QUAD CHARTS:**

  Quad Chart attached.

2. **APPENDICES:**

   Nothing to Report.

Rescuing Warriors from Chronic Pain: A Battlefield-to-Post-Deployment Means to Prevent Opioid-Induced Amplification of Neuropathic Pain from Traumatic Injury

Log number: 14001001
GRANT11775338

PI: Watkins, Linda **Org:** University of Colorado-Boulder **Award Amount:** $500,000

Study Aims

Aim 1. Define if, as expected, commonly used opioids amplify later neuropathic pain when administered early after trauma

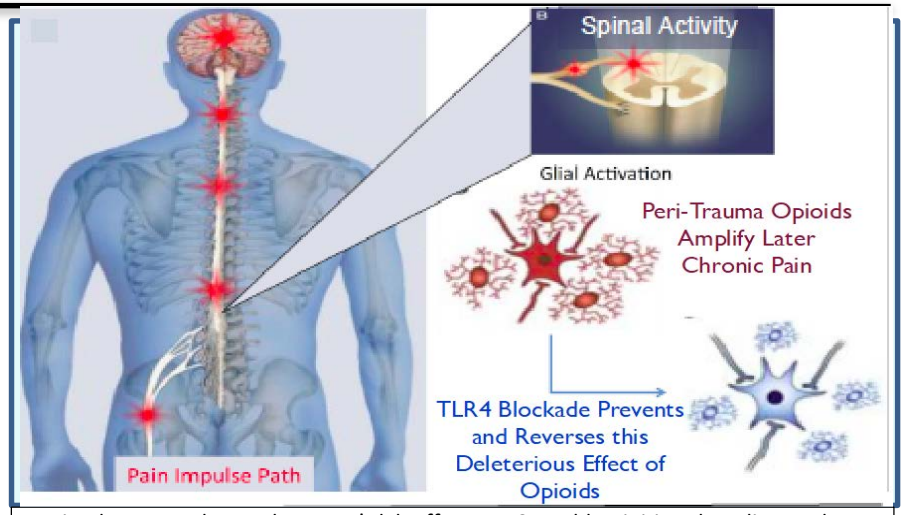
Aim 2. Define if, as expected, commonly used neuropathic pain therapeutics amplify pain when dosed either upon first expression of neuropathic pain or when pain is well established

Aim 3. Prevent these effects by targeting TLR4 signaling

Aim 4. Extend to other measures of recovery from disability

Approach

This is a study in rodents extending our striking data to date, documenting a rarely considered, but now clinically observed, marked long-term deleterious effect of opioids administered in the early post-trauma period, namely an enduring amplification of neuropathic pain. We utilize a widely accepted rodent model of neuropathic pain to explore the amplification of intensity and duration of chronic pain by opioids. Notably this project explores not just this phenomenon but also clinically relevant means of preventing these deleterious effects of analgesics commonly used in the military.



Trained personnel to replace coPI's lab effort at UC-Boulder, initiated studies, and have made great strides in getting the coPI's lab ready to undertake a significant portion of the project at MD Anderson/Texas thereby expediting project performance

Timeline and Cost

Timeline and Cost

Activities	YEAR 1	2	3
Aim 1			
Aim 2			
Aim 3			
Aim 4			
Estimated Budget ($K)	$500K	$500K	$500K

Goal 1: Define if, as expected, commonly used opioids amplify later neuropathic pain when administered early after trauma

Goal 2: Define if, as expected, commonly used neuropathic pain therapeutics amplify pain when dosed either upon first expression of neuropathic pain or when pain is well established **Goal 3:** Define whether targeting toll-like receptor 4 (TLR4) signaling with clinically relevant drugs can prevent the deleterious effects of analgesics documented in Goals 1 and 2

Goal 4: Extend these assessments to other behavioral indices of recovery from disability (voluntary exercise, stamina and agility tests) which may reflect more rapid readiness to return to duty

Comments/Challenges/Issues/Concerns

- As noted previously, the Watkins lab is required to move buildings this winter/spring so there will be an inherent slowly of activity as this transition occurs

Budget Expenditure to Date

Projected Expenditure: $750,000
Actual Expenditure: $530,748